January 12, 1954

Dr. Francis J. Ryan
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Dear Francis:

Thank you for giving me the opportunity to scan your paper which records a very interesting observation. I thought it would be gratuitous for me to attempt any detailed criticism of content and style, but I hope you will forgive a few marginal comments that I scribbled in. The following points occurred to me and might be of some interest to you by way of comment.

On page 8, paragraph 3, I think the argument may not be clear to the uninformed reader. I assume that you mean that, if mutants occur with highest probability in the delayed cells, and that these delayed cells are only a small fraction of the total population, then there will be the apparent correlation.

Page 11: Esther and I have especially looked for transient mutational instability after ultraviolet treatment in the Lac system and found no evidence of it. Reference: page 435 of our 1951 Cold Spring Harbor paper. Esther also made a point of looking for this kind of instability in reverse mutations from Lac- to Lac+ and again the results were completely negative. However, these mutations were spontaneous reversions.

Page 12: I am willing to admit delayed mutation as a possible explanation of Witkin's result, but I would not too hastily discard the possibility of internal recombination, especially as there seems now to be evidence of the fertility of strain B, at least under certain conditions. Reference: discussion of Witkin's Cold Spring Harbor paper.

Footnote 24: I agree with you fully on the inadequacy of the Demerec - Cahn argument, in fact their very assay methods are highly suspect. Elise Cahn used to tell me that there were several situations where there was a very pronounced non-linear dilution in the assays of many of the mutants.

I was surprised to find no specific reference to Bernie Davis on the question of the phenomic barrier discussed on page 5. Davis did find an effective barrier under conditions which seem very similar to yours. Have you had any opportunity to discuss this paper with him?

My own results have made me quite sympathetic to the general conclusions expressed in this paper. There is one point that may have been overlooked in discussions of these specific delays, mainly that they may affect not the immediate division of the treated cell, but the daughter cells of the first or immediately succeeding divisions. One might then argue that it is within the delayed subclones that the mutational events are most likely to occur. We have had some explicit evidence of such subclonal effects in studies on UV treatment of diploid E. coli. See, for example, page 428-429 of the 1951 C.S.H. paper.

I do not recall at the moment whether I put this discussion into print but I may also have recorded this view somewhat more extensively in other discussions in that volume. At any rate, this notion might well clear up the paradox between the apparent absence of delay in most of the bacteria as compared with the very obvious delay in the development of the mutant subclones as indicated in your experiments. The cytological pictures (see, e.g., our 8b and 9b figures in the C.S.H.) are very much in accord with this notion, also.

Of course you may quote me on the dominance of phage susceptibility over resistance but you do not have to resort to an "unpublication." The matter is discussed at some length in the 1949 Proceedings paper in Annual Review of Microbiology, 1949, pages 2-3, and page 8 will interest you also, and volume 61, pages 549-550. Anyhow, I do not think that MGB should be cited in any way as the basis on which authors have been led to contribute their letters to it has been that it is not a publication. Why not just say "personal communication" without citing the bulletin.

I would question your professed disinterest in scions but as an Irishman you seem to be doing pretty much as well as you could have hoped as a latter-day Englishman. Tom has your message--says he is happy.

Sincerely,

Joshua Lederberg

/mg

PSS: V, compounds
Dictator mach.
Single cell primary hybrids
are complete, so again, elimination is post-zygotic.